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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,563	05/02/2002	Dan L. Eaton	P3230R1C001-168	9765

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GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,563	EATON ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.a.D

RESPONSE TO AMENDMENT

The response and amendment filed 3-21-05 has been entered into the record. Claims 1-3, 9 and 10 have been cancelled. Claims 4-8 and 11-17 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Information Disclosure Statements

Applicants argue that the patent number was a correction of a typographical error and the patent as secondarily submitted should be considered without the requisite fee. This is not persuasive, it is a new Patent number and could have easily just been viewed as the typographical error in the Inventor's name. This is a new citation and was not properly considered. Since, Applicants are no longer requred to submit copies of Patent Documents and they are not scanned into the Image File Wrapper, it is the cited Patent Number that is now relied upon. Therefore, the patent number is a new citation of a different patent. Applicants are indeed submitting a new patent for consideration. The examiner cannot ascertain what paper copy was actually filed because US Patents are not scanned into the Image File Wrapper.

Objections/Rejections Withdrawn

The objection to use of the trademarks is withdrawn based on Applicants' amendments.

The rejection of claims 1-6 and 12-13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn based on Applicants' amendments.

Rejections Maintained

Priority

Applicants argue that the nucleic acids have credible, specific and substantial utility and that they are entitled to the priority date of 9-10-98 of provisional document 60/099,812. The provisional document does not provide written description of the claims as now set forth for reasons made of record and only describes SEQ ID NO:56. The provisional document fails to establish utility and enablement for the now claimed polypeptides in any of the priority documents for reasons made of record herein. Description of the protein of SEQ ID NO:56 in the provisional application does not provide compliance with 35 USC § 120 for reasons set forth in the previous office action of record and reasons set forth herein. Applicants are not granted priority for the provisional document 60/099,812.

Applicants maintain the argument that the data in Example 18 (tumor versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8-24-00. This is not persuasive, the priority document does not comply with 35 USC § 120, written description, utility and enablement for reasons set forth in the previous office action of record and reasons set forth herein. This relied upon utility is not a substantial utility for reasons made of record and argued herein.

The priority date is the instant filing date of 5-2-02.

Claims 4-8, and 11-17 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility is maintained for reasons made of record.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that the requirement for a substantial utility defines a "real world use" and cite *Brenner v Manson*, 383 US 519,534(1996) already of record. Applicants argue that MPEP 2107.01 that states that office personnel must be careful not to interpret the

phrase "immediate benefit to the public" or similar formulation to mean that products or services based on the claimed invention must be "currently" available to the public. This is not persuasive, the rejection set forth did not require "current public availability", but a specific and substantial utility for the now claimed invention. Applicants argue that any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial utility". This is not persuasive, the relied upon utility (increased nucleic acid levels in normal tissue as compared to compared to melanoma) specifically requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use and as such is therefore not a "substantial utility" (see MPEP 2107.01(1)). Applicants argue that the USPTO must establish that it is more likely than not that one of skill the art would doubt the truth of the statement of utility, namely that the gene encoding the polypeptide is differentially expressed in certain cancers compared to normal tissue and useful as a diagnostic tool. The argument has been fully considered, but is not persuasive. Utility requires that the skilled artisan be able to use the claimed invention. The specification does not provide a specific and substantial or a well-established use. Applicants have provided a single analysis of nucleic acid without any relative range for basing a utility of alleged over-expression for the claimed protein(s) in normal tissue. There is no guidance on how to use this information for protein levels. No levels (relative or absolute) of the claimed polypeptide are particularly disclosed. Applicants argue that if the gene is differentially expressed in cancer versus non-cancer tissue, then its mRNA and encoded polypeptide are useful as diagnostics. This argument is pertinent to the instant claims because of the functional limitation added wherein the nucleic acid encodes a polypeptide that is over expressed in tumor tissue as compared to normal. The argument has been fully considered, but is not persuasive. If one cannot use the encoding nucleic acid as a diagnostic tool for tumors, then one cannot use the encoded polypeptide either. Additionally, there is no data regarding protein expression in any

tumor as compared to the control in the specification and Applicants are attempting to rely upon a correlation of increased mRNA levels of SEQ ID NO:55 with increased protein levels (SEQ ID NO:56). Applicants argue that the standard for utility is not a mater of statistical certainty, but "more likely than not" and "reasonable probability". Applicants again rely on an asserted reasonable probability of the correlation of mRNA levels with protein levels. This again is not persuasive, the record establishes that one skilled in the cancer diagnostic art would not find it "more likely than not" that the mRNA levels correspond with the protein levels, see Haynes et al, Pennica et al, Gokman-Polar et al and Lewin et al. Applicants argue the court holdings in *Fujikawa v. Wattanasin*, 93 F3d. 1559, 39 USPQ 2d 1985 (Fed. Cir. 1996) and *Cross v Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed Cir. 1985) that indicate that when the *in vitro* results are general predictable of *in vivo* results establishes a significant probability that in vivo testing for the particular pharmacological activity will be successful. This is not persuasive, there is no claimed pharmaceutical composition and the issue is not correlation of in vitro data with in vivo results. The issue is solely in vitro, and the lack of reasonable correlation between mRNA levels and protein levels. In contrast to *Fujikawa v. Wattanasin*, 93 F3d. 1559, 39 USPQ 2d 1985 (Fed. Cir. 1996) and *Cross v Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed Cir. 1985) this specification does not teach in vitro data for the protein. No levels of the protein are taught, absolute or not. Applicants review the record and indicate that their rebuttal evidence establishes the "more likely than not" standard for utility. The position of the office is that the art of record indicates that there is no reasonable correlation. Applicants merely reiterate their position in pages 18-22 of the response. Applicants again argue that they have established that the gene encoding PRO1027 polypeptide is differentially expressed and thus rely again on the "reasonable correlation" of mRNA expression with protein expression. This again is not persuasive Haynes et al. is cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (pg.

1863) and specifically teach "These results suggests that even for a population of genes predicted to be relatively homogenous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of corresponding mRNA transcript." (page 1863, column 1, section 2.1). Haynes et al teaches "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts. " (see page 1870, column 1, Concluding Remarks). Therefore, the skilled artisan immediately recognizes that, at the time of the invention, that no direct correlation between gene amplification/mRNA levels and increased polypeptide levels exists, no dogma exists between mRNA and polypeptide levels (for which neither are disclosed within the instant specification for PRO1411). Applicants again point to the Declaration of Dr. Grimaldi that clarifies the use of pooled samples. This again is not persuasive, it does not establish the particulars of individual variation and statistical significance of individual variation. Diagnostic assays do not use pooled samples. Further, no evidence is proffered to support the opinion that the use of pooled samples "is more likely to be accurate than data obtained from a single individual". Applicants note that many protein based diagnostics in the art in which the level of a particular protein is assessed to determine whether a patient is suffer from a particular condition do not require a normal sample because initially a normal range of protein levels are defined and the patient sample is quantitated to determine whether it is outside of the normal range. This is not persuasive, this specification does not define a normal range for PRO1027 or any variant thereof. Pooled samples do not establish a normal range, they are a single data point. Range is established using multiple samples and this specification lacks any statistical analysis of range for either the nucleic acid or corresponding protein. Applicants argue that the semi quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over-espressed or under expresses in tumor versus normal tissue. Mr. Grimaldi declares that the results of

Example 18 reflect at least a 2-told difference in cDNA between tumor and normal counterpart. It is noted that the details of the semi-quantitative analysis described by Declarant Grimaldi are not detailed in the specification as filed nor is the "at least 2 fold difference" of the declaration. The specification only teaches "more highly" and does not indicate that "more highly" is at least a 2-fold difference. Applicants Exhibit 1 with respect to the visibility of a two fold difference in DNA mass using ethidium bromide staining is noted and provides evidence that an at least 2 fold difference can be observed for 61 ng and 124 ng DNA. However, the declaration remains not persuasive, because the cutoff of the assay as at least 2-fold is not established in the specification as filed for "more highly expressed". So while a 2-fold may be able to be observed, the specificaiton does not establish this as the criteria used at the time of filing. Applicants argue that the precise levels of gene expression are irrelevant, merely that they levels of tumor and normal are different. This is not persuasive. The differences have to be reproducible and statistically significant and moreover, the levels are extremely important as it relates to the correlation of mRNA with protein expression. As previously set forth, given the evidence presented by Haynes et al, Gokman-Polar et al and Lewin, it is clear that one skilled in the art would not assume that a small increase/decrease in mRNA would correlate with corresponding changes in polypeptide levels. In view of the totality of the evidence of record, one skilled in the art would not assume that gene expression (mRNA) necessarily parallels or is predictive of protein expression and would have to perform further experimentation to verify or rule it out. As such, this further experimentation indicates that the asserted utility is not "substantial". It is noted that the literature supports the position of a lack of correlation of gene amplification, mRNA levels and protein expression and specifically cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Nevertheless, gene amplification , is not equivalent to gene expression (i.e., mRNA), which is not the same as polypeptide data (i.e., as claimed). Applicants argue that they have

established that it is the accepted understanding in the art that there is a direct correlation between mRNA levels and the level of expression of the encoded protein. This specification does not teach the expression level of the claimed protein, nor is it demonstrated scientifically statistically significant. The means and methods of sample collection and specifics with respect to data analysis are not set forth in the specification as filed. Therefore, the art indicates that it is not the norm that increased/decreased gene transcription results in increased/decreased polypeptide levels and the asserted utility of the PRO1027 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. The need for further research to reasonably identify or confirm a utility is not "substantial" because it does not identify a "real world" utility (MPEP 2107.01(1)). Applicants argue that a cursory inspection of Figure 1 shows a clear correlation between the mRNA levels and protein levels measured. This is not persuasive, it contradicts the conclusions of the authors that specifically state "no strong correlation between protein and transcript levels" (page 1871, column 1, section 2.1). Applicants indicate that Haynes et al does not teach the absence of such a correlation. This is not persuasive Haynes et al teach "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts." Haynes et al is cited to specifically teach, at the time the invention was made, one of skill in the art would not have reasonably believed to the argued standard "more likely than not" that protein levels were increased. Applicants argue that the 50 fold variation of Haynes does not establish that the correlation is not "more likely than not". This is not persuasive, it was cited to demonstrate even given a very large variation that the protein levels do not reasonably predictably follow. The variation is huge, and according to the declarations the alleged observed difference in nucleic acid was at least 2-fold. Haynes et al specifically caution about drawing conclusions of protein levels based

on transcript levels... indicating that there is no strong correlation. This is in fact defeats the assertion that there is a strong correlation by Applicants (i.e. "more likely than not"). Applicants have not presented any declaratory or other evidence establishing the correlation of levels for the mRNA of SEQ ID NO:55 and the protein levels of SEQ ID NO:56 *in vitro*. Applicants argue that the variability of Haynes et al is due to variability of measuring low levels of mRNA and cite Gygi et al page 1727. This is not persuasive, Gygi et al specifically teach "the correlation between mRNA levels and protein levels was insufficient to predict protein expression levels from quantitative mRNA data" (see page 1720, abstract). Applicants argue that the need for quantitative data is irrelevant since it is the differential expression that is important. This is not persuasive, if the assay for mRNA is so variable as argued by Applicants and allegedly supported by Gygi et al, then given the single assay of Applicant in Example 18, how is the skilled artisan able to predictably diagnose. Is the difference real if the assays are so variable ? Without multiple independent samples and levels it is impossible to ascertain any variability in the instant assay. Since the levels of the mRNA are not reported in the specification it is impossible for the skilled artisan to ascertain any variability that would apply to the instant case. However, given the known variability, the lack of teaching of inter-sample and inter-assay variability in the specification, the single point assay, it is impossible to conclude protein levels from mRNA levels. Further, Gygi et al teach that "We therefore expect that the correlation for all yeast proteins or for random selection would be less than 0.4" Less than 0.4 is less than "more likely than not". Further, Gygi et al indicate that "The observed level of correlation between mRNA and protein expression levels suggests the importance of posttranslational mechanisms controlling gene expression. Such mechanisms include translation control (15) and control of protein half-life (33). Since these mechanisms are also active in higher eukaryotic cells, we speculation that the is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells. " Gygi et al acknowledge potential issues with respect to measurements in

both the mRNA and protein of the report. However, the conclusions remain the same. Applicants argue that Haynes et al teach that the art either implicitly or explicitly assume that for specific genes the transcript levels are predictive of protein levels. The teachings of Gygi et al indicate that this assumption is FALSE that for any random polypeptide the correlation likely approximates 0.4 (less than the 0.51, more likely than not standard). Since, the absolute levels of Applicants mRNA and protein are not established in the specification or by declaraton and it is not clear what category that they fall. Nonetheless, Haynes et al and Gygi et al clearly establish that the assumption of the art is FALSE. Applicants argue that Lewin et al teaches that that the overwhelming majority of regulatory events occur at initiation of transcription. That is the regulatory events in gene transcription not in protein expression/translation and steady state levels. The issue here is protein levels. Applicants argue that Gokman-Polar et al, in contrast to the position of the office, teaches a general trend the mRNA levels predict protein levels. This is not persuasive, Gokman-Polar et al concludes "the small alterations in mRNA expression for these PKC isoenzymes do not correlation with the dramatic changes in expression of the corresponding protein." (page 1378, column 2). Thus, the conclusions of Gokman-Polar are contrary to Applicants position. Further, the data at page 1379, Figure 6 and 7 show an apparent at least two fold difference in QRT-PCR products, does not correspond to similar difference is protein production. A "trend" is not established and indicates that visible fold differences in PCR-products do not correlate with the corresponding measured protein level. Applicants argue Pennica et al and Konopka et al are not relevant to the instant case. This is not persuasive, all the references address the alleged dogma of the art gene copy number = mRNA copy number = protein copy number. Pennica and Konopka et al were cited to teach that gene copy number = mRNA copy number to dispute alleged dogma of the art from all its perspectives. Hu et al was cited to teach that a correlation with disease causality is not established with differences less than 10-fold differences in mRNA expression. This is important to the instant utility because, the specification

specifically indicated that one of the utilities was to use the protein as a therapeutic. In order to use a protein as a therapeutic it must have some established relationship to tumor formation or lack thereof. In this case, since the specification is devoid of absolute levels of mRNA or protein, Hu et al was used to indicate that mere alleged 2-fold increase in mRNA does not establish a role for the protein in tumor formation. Applicants' response focuses on the use of the mRNA and protein for diagnostic purposes and appears to have abandoned this asserted utility in the specification. Applicants also assert the second opinion declaration of Dr. Grimaldi, that those who work in this field are well aware in the vast majority of cases, when a gene is over-expressed... the gene product or polypeptide will also be overexpressed and this same principle applies to underexpression. This again is not persuasive, it is an opinion that is specifically rebutted by Haynes et al of record. The office did not dismiss the "opinion" declaration out of hand but the opinion is contrary to the conclusions of Haynes et al, which relies upon experimental data. As such, without evidence particular to the claimed protein and in view of the relied upon teachings of Haynes et al, the declarations of Dr. Grimaldi are still not persuasive. Haynes et al does in fact refute and rebuts the opinion of Dr. Grimaldi. The same position is taken with respect to the declaration of Dr. Polakis. Haynes et al and Gygi et al establishes that there is no strong correlation of mRNA levels with protein levels and specifically conclude that protein levels cannot be accurately predicted from mRNA levels. Dr. Polakis does not provide any evidence to support his opinion and does not provide any evidence with any particularity to the claimed polypeptide. Applicants draw different conclusions than specifically recited in Haynes et al and Gygi et al. The opinion declaration of Dr Grimaldi and Dr Polakis are in contrast to the conclusions of Haynes et al and Gygi et al of record. Therefore, in the absence of specific particular evidence to the contrary directed to the claimed polypeptides, Haynes et al and Gygi et al are deemed to properly rebut and question the accuracy of the opinion of Dr. Grimaldi and Polakis in the respective declaration. The declarations, in contrast to Applicants position, did not provide any

evidence or facts. Applicants argue that the revised interim guidelines establish that proteins that are differentially expressed in cancer have utility for diagnosis. This is not persuasive, it remains to be established that the claimed proteins are differentially expressed. Applicants argue that Alberts et al (1994) establish that for most genes transcriptional control is predominant. This is not persuasive, Hanyes et al and Gygi et al specifically refute the dogma and indicate that in contrast to the state of the art in 1994, it is recognized that the "multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products and reveal their correct identities and amounts." This was the state of the art in 1998. The broad sweeping conclusions of the art are not supported by careful evaluation and study of Haynes et al and Gygi et al. Applicants argue Zhigang et al that established as correlation of mRNA production and protein production in diagnosis and treatment of human prostate cancer. Zhigang et al does what applicants have not done for SEQ ID NO:55 or 56, a mRNA and protein analysis in multiple samples to establish such a correlation. Again, this is not persuasive in view of Hanyes et al and Gygi et al of record, which establish that for any random mRNA there is no "more likely than not" standard with protein amounts. Applicants argue that the fundamental principal of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells and cite Meric et al. While this may be true, Hu et al teach that small differences in levels of mRNA does not predict any role in cancer formation or generation and therefore it is not understood how such a finding can be used for cancer therapeutics as asserted. The differences in transcript levels or protein levels have not been reported in the specification. Therefore, this specification fails to establish a role for SEQ ID NO:55 or 56 in carcinogenesis. Applicants provide no evidence for a role in carcinogenesis (i.e. more highly expressed in tumor as compared to normal). Applicants again extensively review the previous issues of record at pages 26-31 but add nothing new. These references were considered and were not found to be persuasive for reasons made of record. Applicants

review the declaration of Dr. Ashkenazi that teaches that in situations where protein overexpression does not parallel gene amplification in certain tumor cell types but not others, the protein enables more accurate tumor classification and hence better determination of therapy. This is not persuasive, such is not a contemplated utility of the specification and even if it was, there is no teaching of how to perform any of the asserted use for classification or determination of therapy. Applicants hypothesize that if the gene is amplified but not the corresponding protein, then the clinician accordingly will decide not to treat a patient with agents that target that gene product. This is fundamentally flawed, the specification does not teach agents that target the gene product and therefore how could any clinician make any choice of tumor classification and therapy options based on this specification? Applicants continue to maintain that differential expression is that which provides for utility of the present invention. However, it is maintained that mRNA levels are not predictive of protein levels and the state of the art in 1998 provides evidence that substantiates that conclusion. Applicants have not provided any evidence in particular to the claimed invention and instead seek to establish that at the time that the invention was made that it protein expression more likely than not followed mRNA levels. This is not persuasive for all the reasons made of record. Applicants argue that Hanna et al supports the position of Dr. Ashkenazi that indicates therapy is chosen based on the presence or absence of the Her-2/neu protein. This is not persuasive, Hanna et al along with the art cited therein have clearly and unambiguously taught a role for Her-2/neu in certain breast cancers, a teaching that this specification is lacking. This specification is devoid of such information with respect to the claimed protein and melanoma. Applicants assert that Konapka et al provides evidence of the correlation of mRNA levels with protein levels. This is not persuasive, Konopka et al makes no such generalization and in contrast the teachings of Haynes et al and Gygi et al make general conclusions opposite to that provided by Applicants. Applicants again argue a presumption of utility and no need to absolutely prove the asserted utility is real and only

evidence needs to be reasonable indicative of the asserted utility. This is not persuasive, for all the reasons previously set forth. Haynes et al and Gygi et al established that the evidence is not reasonable indicative, nor "more likely than not". Applicants argue that the PTO has not provided a *prima facie* case, and even if it had the submitted evidence and declarations are sufficient to overcome the *prima facie* case. It is maintained a *prima facie* case has been established and that the proffered evidence is insufficient to obviate the prima facie case of lack of utility for the protein. Applicants argue that the declaration of Dr. Grimaldi establish that the date in Example 18 are real and significant. This again is not persuasive for all the reasons made of record. Applicants again argue that it is well established in the art that a change in mRNA levels heralds the same change in protein levels. This is not persuasive, the art of record specifically teaches that the two are not inexorably linked, nor meets the "more likely than not" in view of the teachings of Haynes et al and Gygi et al of record. The assertion of a diagnostic is not found to be substantial. There no evidence that the claimed polypeptides are differentially expressed and that such expression is statistically significant across multiple samples as is requisite for a diagnostic utility. Applicants argue the standard of clear inoperability for the entire claims and if it is minimally useful for achieving a useful result a rejection of the claimed invention is not warranted. This is not persuasive. No minimally useful result has been provided with respect to the claimed protein(s). In view of the totality of the record, the lack of any particulars with respect to the claimed polypeptides, the teachings of Haynes et al and Gygi et al, it is found that it is not reasonable to conclude that protein levels can be predicted from mRNA levels. In summary, the instant specification provides a mere invitation to experiment for establishing a specific and substantial use for the claimed polypeptides, which does not reasonably extrapolate to a readily available utility. The rejection is maintained.

Claim 4-8 and 11-17 stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for reasons made of record.

Claims 4-5 and 12-17stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons made of record in the first office action on the merits mailed 6-15-04.

Applicants' arguments have been carefully considered but are not persuasive. Applicants review the standard for written description. The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Applicants rely on the level of knowledge and skill in the art and the teachings provided by the specification and assert that the inventor is not required to teach every single detail of the invention. This is not persuasive, the teachings must provide conception by way of written description for the claimed genus. As previously set forth, a single polynucleotide and a single polypeptide does not provide support for conception of variants period. The specification contemplates that the polypeptides can be a homolog in other species or human variants as isolated from nature. This specification fails to teach any variation of SEQ ID NO:56 or fragment thereof that complies with either of those contemplated situations. Applicants have not provided a representative number of species by way of written description to support possession of the genus of variants now claimed. The instant situation is not analogous to Example 8 of the written description guidelines because the claims were

limited to a particular sequence that had 95% identity to known ligases and the assertion that the limited sequence was a ligase. This is quite different than the instant case is drawn to a polypeptide that has variation and only a single member is disclosed, with no known consensus sequence. The disclosure of a single polypeptide does not warrant genus claims. Applicants were not in possession of a genus. Applicants neither isolated, cloned or otherwise identified variants that fell within the genus. The skill in the art does not change this fact. There are no other disclosed nucleic acids or polypeptides that fall within the genus and meet that claimed functional criteria of encoded by a polynucleotide that is more highly expressed in normal skin tissue as compared to melanoma or the isolated polypeptide or fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:56 in skin samples. Applicants also assert that the claims are analogous to the claims discussed in Example 14 of the written description training materials. The instant activity is distinguished from Example 14, because the claimed activity is not catalytic and the neither the specification nor the art provides for a correlation of structure with the claimed functions. The written description does not provide any such functional correlation. The sole single *human* polypeptide species described is PRO1027 of SEQ ID NO:56. No written description is provided in the specification for any other species of PRO1027 molecules, in which disclosure of a single "human" polypeptide sequence (*which the claims are not limited toward*) does not reasonably constitute "the claimed genus of polypeptides". Analogous to the situation decided in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), "an adequate written description of a DNA [product] requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself". *Fiddes v. Baird*, 30 USPQ2d 1481, 1483 (1993) held that claims directed to mammalian FGFs were found unpatentable due to lack of written description for the broad class, in which the specification had provided an adequate description of only the bovine sequence. Similarly, only the single *human*

polypeptide specie of SEQ ID NO: 56 has been described in the instant specification. Accordingly, the court held in *Univ. California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) that: "One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is". and that: "A description of a genus of cDNAs [products] may be achieved by means of a recitation of a representative number of cDNAs [products], *defined by nucleotide sequence*, failing in the scope of the genus or of a recitation of structural features common to the members of the genus, *which features constitute a substantial portion of the genus* [emphasis added]. This is analogous to enablement of a genus under 112, [first paragraph], by showing the enablement of a representative number of species within the genus. See *Angstadt,* 537 F.2d at 502-03, 190 USPQ at 218". A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between the biological function and the structure of the sequence is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. *In re Bell* F.2d 781, 26 USPQ2d (Fed. Cir. 1993). This specificaiton provides, an invitation for others to discover a representative number of species with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics has not reasonably been provided within the instant specification. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed. See for example *Fujikawa v Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of the a genus because it would not "reasonably lead" those skilled in the art to any particular species. In the instant case, while the skilled artisan may envision may changes to the polypeptide of SEQ

ID NO:56, one can not envision what changes to the structure or what part of the structure of SEQ ID NO:56 are conserved as it correlates with the now claimed properties. The specification provides no guidance and does not set forth a representative number of polypeptides with the claimed property to allow the skilled artisan to envision the genus and the distinguishing identifying characteristics of the now claimed genus. Thus, Applicant was not reasonably in possession of the "claimed genus of polypeptides" encoded by a genus of cDNA molecules, or raise antibodies for the reasons previously made of record. Applicants argue other patents issued by the office to variants or nucleic acids or proteins when Applicants did not actually make them. This is not persuasive MPEP 2100 specifies that certain issues are resolved on a case by case basis (utility, anticipation, obviousness, compliance with written description requirement) and it is well settled that whether similar claims have been allowed to others is immaterial. See *In re Giolito*, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and *Ex parte Balzarini* 21 USPQ2d 1892, 1897 (BPAI 1991).

Claims 4-7, 11, 12 and 14-16 stand rejected under 35 U.S.C. 102(b) as being clearly anticiapted by Rhodes et al, (Database sequence, publically available May 1, 1999) is maintained for reasons made of record for claims 1-11 in the previous office actions of record.

Applicants arguments have been considered but are not persuasive. Applicants again argue their priority date. The priority date has not been granted for reasons made of record. The Stemple Doctrine and *In re Moore; In re Pit and Bender* 170 USPQ 260, (CCPA1971) are specifically directed to sufficiency of an affidaviat filed under 37 CFR 1.131 to overcome a rejection based specifically on a 102(a) or 102(e) reference. It does not address 102(b) statuatory bars. A 102(b) reference is a "statuatory bar", for which neither the "Stempel Doctrine" nor a declaration persuant to 37 CFR 1.131 can overcome.

37 CFR 1.131 specifically states that "Prior invention may not be established under this section if either:

(1) The rejection is based upon a U.S. patent or U.S. patent application publication of a pending or patented application to another or others which claims the same patentable invention as defined in § 1.601(n); or

(2) The rejection is based upon a statutory bar."

Since the rejection is a statuatory bar, a declaration persuant to 37 CFR 1.131 upon which the Stemple Doctrine and the decision in *In re Moore* et al is based, can never be persuasive.

New Rejections Based on Amendment

Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specificaiton as filed does not apparently have support for the now recited function of "isolated polypeptide or fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:56 in skin tissue samples. While the applicants have support for antibodies that specifically bind SEQ ID NO:56, there is no explicit support for using variant proteins to generate antibodies that cross-react with SEQ ID NO:56. Further, such a concept is exactly opposite of that expressed by the definition of "specifically binds" in paragraph [0247] at the bottom of page 42. If an antibody is specific for a polypeptide sequence then it cannot by definition bind the variant sequence or be cross-reactive. The antibody by definition will bind the variant because it was used to make the antibody. Therefore, there appears to be no implicitly or explicit support for generation of cross-reactive antibodies that are

"specific" because the concepts are mutually exclusive in view of the definition of specifically binds in the specification. Even if the term "specifically binds" was removed, the concept of using variant polypeptides to generate antibodies that bind another sequence (i.e. that are cross-reactive) is not conveyed by the specification as filed. Applicants pointing to the pages of the specification where implicit or explicit support can be specifically found for this claim limitation best resolve this issue.

Status of Claims

Claims 4-8 and 11-17 stand rejected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy

Primary Examiner

Art Unit 1645